## REMARKS

Claims 2-4, 12, 13, 18-21 and 27 were rejected, and claim 16 was objected to. Claim 18 is amended herein to correct a minor typographical error. Claims 2-4, 12, 13, 15-21 and 27 are pending, and claims 15 and 17 are allowed.

### Formal Matters

Applicants gratefully acknowledge the reopening of the prosecution of the instant application and the entry of the Amendment filed June 2, 2003 (Paper No. 59).

Applicants also gratefully acknowledge the apparent withdrawal of the rejections under 35 U.S.C. § 103 (a) over Olsson (U.S. Patent No. 5,073,540) or Krensky (WO 88/05784).

Claim 16 was objected to in the Action as depending from a rejected claim, *i.e.*, claim 27. Applicants respectfully request that the arguments provided below demonstrate the allowability of claim 27 and its dependent claims, thereby rendering the objection moot. Therefore, Applicants request that the objection be withdrawn.

### Rejection Under 35 U.S.C. §103 (a)

Claims 2-4, 12-13, 18-21 and 27 are rejected under 35 U.S.C. § 103 (a) as allegedly being unpatentable over WO 88/05784 (Krensky) in view of Wong *et al.* (*Human Immunol.* 35:200-08 (1992)), U.S. Patent No. 5,073,540 (Olsson) and U.S. Patent No. 5,478,925 (Wallach). According to the Action, it would have been *prima facie* obvious to one of ordinary skill in the art to modify the prior art peptides taught by Krensky as multimers as is taught by Wallach for other receptor mimicking and inhibiting peptides, and to test functional activity on surface receptors or lymphocyte activity of the modified peptides using assays taught by Krensky and to use the said multimeric peptides in the method of inhibiting graft rejection as taught by Krensky. The Examiner asserts that it would have been obvious to prolong graft survival time by reducing the rejection caused by CTL which comprise TCR that aggregate upon binding to MHC class I molecules taught by Wong. Claims 2-4, 12, 13, 18-21, and 27 are also rejected under 35 U.S.C. § 103 (a) are allegedly being unpatentable over WO 88/05784 (Krensky) in view of U.S. Patent No. 6,419,931

(Vitiello). According to the Examiner, the Vitiello teaches that peptides that modulate CTL can be combined to form multimers and that the same peptide can be linked to itself to form a homopolymer. Applicants traverse these rejections.

**I. Krensky in view of Wong, Olsson, and Wallach**

A. The cited combination of references fails to teach or suggest every element of the claimed compositions.

Applicants respectfully submit that the cited combination of references fails to render the claimed methods *prima facie* obvious because the combined references lack any teaching or suggestion regarding the use of dimers of HLA peptides to inhibit CTL activity and prolong graft acceptance. As acknowledged by the Examiner, Krensky lacks any teaching or suggestion regarding dimers of HLA peptides. Olsson, Wallach, and Wong fail to cure this deficiency. Thus, the combined references lack any teaching or suggestion regarding HLA peptide dimers in the claimed methods.

Olsson, Wallach, and Wong fail to teach or suggest the use of HLA peptide dimers when combined with Krensky alone. Olsson lacks any teaching or suggestion regarding the use of HLA dimers. In fact, Olsson discloses a very different dimer that consists of two peptides originating that bind two different sites. As discussed in the Appeal Brief submitted September 2, 2003, Olsson teaches the use of a very specific heterodimer composed of a HLA peptide and a peptide that binds the binding site of a second cell surface receptor, *e.g.*, a growth receptor ligand, a fundamentally different peptide than that of the instant methods. *See* Olsson, at column 2, lines 29-35. Because Olsson lacks any disclosure regarding the use of dimeric HLA peptides, Olsson fails to remedy this deficiency in Krensky.

Similarly, Wallach fails to teach or suggest the use of HLA peptides in any form. While Wallach teaches the use of dimers (and multimers) to modulate conditions mediated by TNF, such dimers provide no guidance or suggestion to the skilled artisan regarding the HLA dimers of the instant methods. Wallach's dimers involve monomers of at least a significant portion of the extracellular domain of the cell-bound TNF-receptor. Not only are these monomers significantly larger, *i.e.*, 100-200 amino acids or more, than the peptides of the present methods, but mechanistically the oligomerized soluble TNF-receptor mediates its effects in a distinct manner.

These soluble TNF-receptors interact with the soluble cytokine, *i.e.*, TNF, to modulate TNF activity by inhibiting TNF binding to its receptor, while the peptides of the present methods interact with the cell surface receptors to modulate class I interactions. Thus, the design of Wallach's dimers conveys to one of ordinary skill in the art the desirability of modulating cytokine activity by impeding the cytokine binding with its cell surface receptor. Wallach provides no teaching that such multimers are useful in any setting other than cytokine-cytokine receptor interactions. Moreover, Applicants are unaware of any knowledge in the art that would compare cytokine-cell receptor interactions with the interactions targeted by the peptides of the instant methods. Because Wallach's dimers comprise the entire active portion of a cytokine receptor and function in a fundamentally distinct way, they are clearly distinguishable from the dimeric peptides of the instant methods that comprise small peptides from a protein domain that target a different biological interaction.

Finally, Wong contains no teaching that would guide one of ordinary skill in the art to the peptides of the claimed methods when combined with Krensky in view of Olsson and Wallach. Wong does not discuss or suggest the use of peptides to modulate the activity of T cells. While Wong discloses the aggregation of T cell receptor (TCR) with CD8 on PHA-propagated polyclonal T cell line, Wong states unequivocally that the *in vivo* corollaries of the findings are uncertain. *See* Wong, page 207 ("The in vivo corollaries of these findings are uncertain."). In point of fact, Wong discloses no experiments performed with the TCR binding MHC class I molecules. The observations disclosed by Wong are in a completely artificial system, *i.e.*, the TCR and co-receptors are aggregated by antibody in the absence of anchoring surface or secondary linking agents in a T cell line maintained through chronic mitogen activation. It is well known in the art that antibody binding of the TCR in the absence of other co-stimulation molecules can, and frequently does, result in a distinct activation of the T cell, particularly when a polyclonal T cell line is used. This limitation is acknowledged by Wong in the authors refusal to speculate on whether the disclosed data predicts *in vivo* TCR behavior. Thus, the mere disclosure of TCR aggregation in Wong fails to teach or suggest any use or desirability for the peptides of the claimed methods.

In the absence of a teaching or suggestion of the use of HLA peptide dimers, Krensky in view of Olsson, Wallach, and Wong fail to render the claimed methods *prima facie* obvious.

B. The cited references provide no motivation to combine and modify their teachings to result in the claimed methods.

Applicants respectfully submit that there is no motivation to combine or modify Krensky with Olsson, Wallach, and Wong. With regards to Olsson, the reference provides no teaching regarding the desirability of modifying its peptides to result in the peptides of the claimed invention. Moreover, such a modification changes the principle of operation of Olsson's peptides. In other words, such a modification would ablate the ability of the peptides disclosed in Olsson to bind the binding site of a cell surface receptor, and thus rendering the teachings of Olsson (alone or in combination with the cited references) insufficient to render the claimed methods *prima facie* obvious. *See* MPEP § 2143.02 ("If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teaching of the reference are not sufficient to render the claims *prima facie* obvious." (citations omitted) (emphasis added)). Thus, while Olsson teaches the use of dimers, the disclosed dimers consist only of one HLA peptide. The disclosure in Olsson at column 4, line 61 to column 5, line 6 does not extend the teachings of Olsson to HLA dimers. A careful reading of the entire specification reveals that this disclosure is directed to the character of the single HLA peptide useful in Olsson's invention. Applicants submit that the cited paragraph merely discloses the use of alternative regions of the HLA molecule that bind to the cell surface receptor of interest, (*i.e.*, endocrine, paracrine, and autocrine receptors, adrenergic receptors, lipoprotein receptors, opiate receptors, and steroid receptors) other than those already disclosed as the single HLA peptide of the invention. Nothing in the description suggests or even alludes to the use of HLA dimers alone.

Likewise, Wallach contains no suggestion or teaching to modify the monomers of Krensky in view of Olsson and Wang to result in the claimed methods. One of ordinary skill of the art in immunology would not equate a cytokine receptor with a MHC molecule. Moreover, Wallach does not address any aspect of the success of peptides that represent only a small portion of a protein domain. Wallach discloses the use of entire extracellular domains to act as a sink for the cytokine, TNF. The use of only a portion of the TNF receptor as an inhibitory peptide would improperly change the principle of operation of Wallach's invention. *See* MPEP § 2143.02. Wallach's invention allows the soluble ligand, *i.e.*, TNF, to be bound before ever interacting with its receptor. In other words, Wallach's dimers (and multimers) of soluble TNF-receptor act to

indirectly inhibit cytokine binding by providing a separate binding receptor or sink to absorb TNF. Applicants note that such an indirect approach is not available for the interaction targeted by the claimed methods and compositions as no soluble ligand is involved. If a peptide from the TNF receptor, rather than the extracellular domain of Wallach, was used as an inhibitory molecule, however, its likely mode of action would be to directly inhibit cytokine binding through the blocking of TNF binding the TNF-receptor. Such a modification results in a change of the principle of operation of Wallach's invention, and therefore Wallach in combination with Krensky in view of Olsson and Wong fails to render the claimed methods *prima facie* obvious.

Wong fails to provide the necessary motivation to combine Krensky with Olsson and Wallach because Wong contains no teaching or suggestion regarding TCR aggregation on CTL aggregating upon binding class I MHC molecules. Wong does not examine CTL activity. The binding of class I MHC molecules is performed using a completely artificial system, *i.e.*, binding using anti-CD3 antibodies, that the authors acknowledge has questionable relevance to *in vivo* T cell activity. Thus, a person of ordinary skill would have no motivation to make the asserted combination with Krensky, Olsson, and Wallach.

In sum, the no cited reference or any combination provides the motivation or suggestion to modify and combine the teachings of the references to result in the claimed methods. Applicants note that the entirety of each of the references must be considered including any disclosure that teaches away from the invention. *See* MPEP § 2141.02 ("A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention." (citations omitted)(emphasis included)). Thus, the disclosure of these references that teach away from the claimed methods, particularly that of Olsson and Wallach, **cannot** be disregarded or overlooked.

C. The cited references furnish no expectation of success for the claimed methods and compositions.

In the absence of any teaching or suggestion regarding HLA peptide dimers, Krensky in view of Olsson, Wallach, and Wong fail to provide any reasonable expectation of success regarding the claimed methods. Krensky contains no teaching regarding HLA peptide dimers. Olsson discloses only the desirability of a dimeric peptide that binds the binding site of a receptor and an

allosteric site through the Class I MHC peptide, and teaches away from the desirability of using a dimeric peptide that binds a receptor only through non-binding site interactions. Wallach discloses only the desirability of a multimeric protein that binds to a ligand, thereby teaching away from using small peptides that bind a receptor. Wong teaches aggregation of the TCR in an artificial system and unequivocally limits its teachings to the system shown. Thus, Krensky in view of Olsson, Wallach, and Wong provides no reasonable expectation of success regarding the modification of its dimeric peptides to result in the instant dimeric peptide of Class I MHC sequences that bind a receptor through non-binding site interaction.

D. The dimers of the claimed methods do not exert the same functional effects as a monomer.

Applicants respectfully submit that there is no objective evidence that supports the Examiner's continued assertion that the dimers of the claimed methods exert the same functional effects as the monomer. *See* Action dated December 3, 2003, at page 3, last paragraph, and at page 4, sixth full paragraph. The dimeric peptides have unexpected superior properties. Objective evidence disclosed in the instant specification demonstrates the unexpected superior inhibitory effects of dimeric peptides on CTL activity. Specifically, Appellants disclose the results of actual experiments performed with peptide monomers and dimers of Class I MHC sequences on page 22 of the specification, lines 1-9. The experiments can be summarized as follows: While the monomers reduced CTL activity, the inverted dimer B2702.84-75/75-84 and the homodimer B2702.75-84/75-84 were unexpectedly superior to the monomer in their ability to completely inhibit cytotoxicity. *See* specification, at page 22, lines 5-9. In other words, the evidence demonstrates that monomers do not exert the same inhibitory effect as dimers of the same unit on CTL activity because the monomers exerted only a partial inhibitory effect. Appellants respectfully submit this objective evidence disclosed in the specification demonstrates the unexpected superiority of the dimeric peptides relative to the monomeric peptides, and therefore the dimeric peptides are nonobvious. *See In re Soni*, 34 U.S.P.Q.2d 1684 (Fed. Cir. 1995) (holding that what is unexpected to the skilled artisan is not obvious).

**II. Krensky in view of Vitiello**

A. The cited combination of references fails to teach or suggest every element of the claimed compositions.

Applicants submit the combination of Krensky and Vitiello fails to teach each and every element of the claimed inventions because Vitiello fails to teach or suggest the use of HLA dimeric peptides. The peptides of Vitiello are distinct from those of the instant application. First, Vitiello's peptides are designed to induce or stimulate a CTL response. *See* Vitiello, at column 4, lines 15-27. In other words, these peptide bind MHC class I molecules in the antigen binding cleft itself. While Vitiello discloses dimers of peptides, both peptides are designed to stimulate T cell responses with one being directed to stimulation of helper T lymphocytes (HTL) and one being directed to the stimulation of CTLs. Even in the discussion of the use of homodimers, the disclosure is limited to peptides used to stimulate CTL activity. Vitiello lacks any disclosure regarding the use of HLA-derived peptides to inhibit CTL activity. Second, Vitiello's peptides are derived from pathogens, *e.g.*, virus, bacteria, or parasite, or tumors. Vitiello is absolutely silent on the use of HLA-derived peptides or HLA dimers. As acknowledged by the Examiner, Krensky lacks any teaching or suggestion regarding dimers of HLA peptides. Vitiello fails to remedy the deficiency in Krensky, and therefore, the cited combination fails to render the claimed methods and compositions *prima facie* obvious.

B. The cited references provide no motivation to combine and modify their teachings to result in the claimed methods.

There is no motivation to combine Krensky with Vitiello because the two disclosures have opposing purposes. To modify the peptides of Vitiello to inhibit cytotoxicity of CTLs would render the Vitiello peptides unsatisfactory for its intended purpose. *See* MPEP § 2143.01 ("If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." (citation omitted)). Vitiello's peptides stimulate CTL activity by providing a source of antigen, while the instant methods and compositions inhibit CTL activity. Vitiello only suggests the antigenic peptides as inhibitory in an assay system designed to identify antigenic epitopes. *See* Vitiello, at Example 1. Furthermore, modifying the peptides of Vitiello using the teachings of

Krensky would change the principle of operation of the Vitiello peptides because the purpose of the Vitiello peptides are to stimulate a CTL response. *See* MPEP § 2143.01. The fact that Vitiello teaches dimerization is without more insufficient to render the claimed methods and compositions *prima facie* obvious. *See* MPEP § 2143.01 ("The mere fact that reference can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." (citations omitted)). Vitiello's invention does not lie in the mere dimerization of any peptide for any reason. Vitiello's invention and supporting disclosure clearly lies in the identification and use of antigenic peptides that stimulate CTL activity. Thus, one of ordinary skill in the art would not be motivated to combine the teachings of Vitiello with Krensky.

C. The cited references furnish no expectation of success for the claimed methods and compositions.

The combination of Krensky and Vitiello also fail to provide any reasonable expectation of success. Given that the combined references fail to teach every element of the claimed methods and the references have opposing purposes, they do not reasonably convey an expectation of success regarding HLA peptide dimers inhibiting CTL activity.

In view of the above, Applicants respectfully submit that the rejections are overcome and request their withdrawal.

## CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 286002020023. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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